III. REMARKS

A. Priority

Applicant has claimed foreign priority based on Application No. DE 199 30 335.5, filed in Germany on July 2, 1999. Applicant files herewith a certified copy of the priority document, DE 199 30 335.5, as required by 35 U.S.C. 119(b).

B. Claim Objections

Claims 16, 17 and 30 were objected to because of the following informalities: Claim 16 can be clarified, if appropriate, to reflect that the phosphate, fluoride and fluorophosphates salts are salts of calcium by for example changing the claim language "phosphate, fluoride and" to "phosphate salts of calcium, fluoride salts of calcium and." Claim 17 was objected to as being dependent upon a (depends from claim I which is canceled) canceled base claim.

Claim 30 is objected to for not properly following a dependent claim from which it depends. A series of singular dependent claims is permissible in which a dependent claim refers to a preceding claim which, in turn, refers to another preceding claim. A claim which depends from a dependent claim should not be separated by any claim which does not also depend from said dependent claim. It should be kept in mind that a dependent claim may refer to any preceding independent claim. In general, applicant's sequence will not be changed. *See* MPEP § 608.01(n).

Claim 16 was amended as suggested by the Examiner. In response to the objection to claim 30, claim 22 was cancelled and represented as represented claim 31 and claim 30 was cancelled and represented as represented claim 32. Claim 32 is not separated by a claim which does not also depend from claim 32.

1. Claim Rejections Under 35 U.S.C. § 103(a)

Claims 16–22, 28 and 30 stand rejected under 36 U.S.C. 103(a) as being unpatentable over PCT/1B97/01 634 to Rudin et al. in view of United States Patent No. 4,853,225 to Wahlig at al. and further in view of Flautre et al. Journal of Materials Science: Materials In Medicine, Evaluation of Hydroxyapatite Powder Coated with Collagen as an Injectable bone Substitute: Microscopic Study in Rabbit, 7, pgs 63–67 (1996).

Applicants respectfully traverse this rejection by amending claim 16 and the remarks which follow. Applicants submit that claims 16–22, 28 and 30 as amended are not obvious over the prior art cited by the Examiner because none of the cited references alone or in combination, teaches or suggests all the limitations of the amended claims, an element which must be shown in order to establish a prima facie case of obviousness.

In making the rejections of the claims as filed, the Examiner alleged that Rudin et al. teach a hydroxyapatite composite comprising finely divided rod like particles of hydroxyapatite having dimensions of 60nm(L) by 15nm(W) by 5nm(T) on page 2 paragraph 5. Applicants are unable to find such a teaching in Rudin. While Rudin does refer to the physical structure of the hydroxyapatite particles, there is no teaching that these particles are rod like. The closest Rudin comes to teaching rod like particles is in the Abstract where it is taught that being *"The composition comprises hydroxxyapatite in the form of particles of ultra finely divided hydroxyapatite".* There is no suggestion that these ultra finely divided particles are rod like or rodlet-like nanoparticles. The specification contains references to *"particles"* and to *"ultra finely divided"* HA or hydroxyapatite on page 3 paragraphs 4 and 5; on page 5, paragraph 3; and in each of the examples. Such a disclosure does not suggest rod like or rodlet-like nanoparticles. Thus, Rudin teaches only that the hydroxyapatite is in the form of particles that are ultra finely divided but there is no teaching or suggestion that they are rod like or rodlet-like nanoparticles as claimed in the instant claims.

As to the Examiner's allegation that Rudin et al. teach a hydroxyapatite composite comprising finely divided rod like particles of hydroxyapatite having dimensions of 60nm(L) by 15nm(W) by 5nm(T) is concerned, Applicants respectfully submit that the Examiner misunderstood the particle dimensions. The exact text of Rudin's teaching concerning the particle dimensions is:

> A preferred composition having a more pronounced effect in view of the improvements obtained according to the invention comprises particles of hydroxyapatite with an average particle size in length (1), width(d) and thickness(h) of about l = 0.06µm +/- 50%, d = 0.015µm +/- 50W and h = 0.005µm +/- 50
> A most preferred composition having a surprisingly superior effect in view of the improvements obtained according to the invention comprises particles of hydroxyapatite with an average particle size in length (l), width(d) and thickness(h) of l about 0.06µm, d about 0.015µm, h about 0.005µm." (paragraphs 5 and 6 on page 2)

The particle dimensions taught in the paragraphs reproduced above convert to a length (l) of about 0.06µm, a width (d) of about 0.015µm and a thickness (h) about 0.005µm in view of the fact that 1 µm = 1 nm. An enclosed copy of page 17 from CHEMISTRY, by John C. Bailar, Jr. *et al.* shows that the one-to-one equivalence between nanometers (nm) and millimicrons (µm) is well known. Even assuming arguendo that Rudin's thickness is the same as the mean particle diameter of the instant claims, the particles claimed in the instant claims are from 2000 to 60,000 times larger than those taught by Rudin. ($10/5 \times 10^{-3} = 2000$; $300/5 \times 10^{-3} = 60,000$). In view of the foregoing, Rudin does not teach the same particles as claimed in the instant claims.

In making the rejection over the combined teachings of Rudin and Walig, the Examiner admitted that Rudin does not teach the incorporation of a protein, protein hydrolyzate or protein hydrolyzate derivative into a composite of these materials and hydroxyapatite. However, the Examiner cited Wahlig for teaching a hydroxyapatite composition which comprises collagen or from 1–20% of a collagen degradation product (*see* col 4 lines 62–67) which includes gelatin.

Applicants submit that the exact text of Wahlig's teaching at column 4, lines 62–67 is:

> Thus, pulverulent tricalcium phosphate can be compressed with the chemotherapeutic either directly or with the addition of about 1–20% of a **physiologically acceptable binder** which can preferably be absorbed in the body, for example a collagen degradation product, elastin or, preferably, calcium sulfate, to form a medicament depot which, after implantation, initially retains its shape and releases the active compound in a protracted manner, but in the long term is absorbed into the body. (emphasis added).

It is evident from the above that Wahlig teaches that the function of the collagen degradation product is that of a binder whereas the proteinaceous material of Applicants claims forms a structured composite material with hydoxylapatite. Wahlig does not teach or suggest that nanoparticles of the calcium salts are uniformly associated onto the skeleton of the protein component as recited in Applicants' claims as amended. Wahlig also does not teach or suggest a composite wherein rodlet-like hydroxylapatite particles are uniformly associated on the protein skeleton as claimed in the instant claims.

The teachings of Flautre et al. do not add anything to the teachings of Wahlig et al. that would guide the skilled artisan to arrive at Applicants claims as amended. In the last sentence of the Introduction, Flautre teaches that hydroxyapatite is **coated** with collagen forming microspheres (HA + COLL). There is no teaching or suggestion in Flautre of a composite material comprised of rod-like hydroxylapatite particles that are uniformly associated on the protein skeleton.

The Examiner concluded that it would be obvious to one skilled in the art to combine the rod like shaped hydroxyapaptite particles of Rudin at al. with the bio-absorbable collagen and/or gelatine comprising product (see cl 5 lines 14–1 8) excipient of Wahlig et al because both are directed to stomatological uses. Thus, the claimed invention of the composition was within the ordinary skill in the art to make and use at the time it was made and was as a whole, prima facie obvious.

Applicants submit that the claims as amended would not be obvious over the teachings of Rudin in view of Wahlig and in further view of Flautre because a *prima facie* case of obviousness could not be made out. More specifically, a *prima facie* case of obviousness requires (1) There must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP 2143. The third criterion could not be met in the case of the claims as amended. As shown previously, none of the references alone or in combination teaches: (a) rodlet-like hydroxylapatite nanoparticles; (b) having a mean particle diameter of 10 to 300 nm; (c) which are uniformly associated onto the skeleton of the protein component.

2. <u>Double Patenting</u>

Claims 16–22, 28 and 30 stand provisionally rejected under the judicially created doctrine of double patenting over claims 8–10 and 13 of co-pending Application Nos. 09/868,379; 10/465,157; 09/868,379; 10/297,889; and 10/297,842. This is a provisional double patenting rejection since the conflicting claims have not yet been patented. Although the conflicting claims are not identical, they are not patentably distinct from each other because the subject matter claimed in the instant application is fully disclosed in the referenced copending application and would be covered by any patent granted on that copending application since the referenced copending applications and the instant application are claiming common subject matter which was set out in tables of comparison.

Applicants respectfully request that the provisional Double Patenting rejection be held in abeyance until it is made permanent. At that time, Applicants will respond to the rejection.

III. Conclusion

In view of the amendments and remarks above, Applicants ask for reconsideration and allowance of all pending claims. Should any fees be due for entry and consideration of this Amendment that have not been accounted for, the Commissioner is authorized to charge them to Deposit Account No. 04-1406.

Respectfully submitted,

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August 4, 2005

Enclosures:

- Certified copy of Priority Document, German Patent Application No. DE 199 30 335.5, filed July 2, 1999
- Copy of page 17 from CHEMISTRY, by John C. Bailar, Jr., et al., referenced on page 6 of Applicants' Amendment

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Decimal location	Prefix	Prefix symbol
$1{,}000{,}000{,}000{,}000 = 10^{12}$	tera	T
$1{,}000{,}000{,}000 = 10^{9}$	giga	G
$1{,}000{,}000 = 10^{6}$	mega	M
$1{,}000 = 10^{3}$	kilo	k
$100 = 10^{2}$	hecto	h
$10 = 10^{1}$	deka	da
$0.1 = 10^{-1}$	deci	d
$0.01 = 10^{-2}$	centi	c
$0.001 = 10^{-3}$	milli	m
$0.000\,001 = 10^{-6}$	micro	μ
$0.000\,000\,001 = 10^{-9}$	nano	n
$0.000\,000\,000\,001 = 10^{-12}$	pico	p
$0.000\,000\,000\,000\,001 = 10^{-15}$	femto	f
$0.000\,000\,000\,000\,000\,001 = 10^{-18}$	atto	a

Table 2.5
Prefixes for Multiples and Fractions of SI Units
The symbol for the prefix "micro" is the Greek letter mu, μ.

a. Length In both the older metric and the newer SI systems, the meter (m) is the base unit of length. Many very small lengths in chemistry are conveniently expressed in nanometers (1 nm = 10^{-9} m) or picometers (1 pm = 10^{-12} nm). An older unit for very small distances is the angstrom, abbreviated Å (1 Å = 10^{-10} m = 0.1 nm).

b. Volume Because of the relationship of length to volume (as illustrated above), the SI derived unit for volume is the cubic meter (m^3). (The SI unit for area is the square meter, m^2.) On this basis, the recommended replacement for the liter (L), the volume unit in the older metric system, is the cubic decimeter (1 L = 1 dm^3). However, the liter and the milliliter (mL) remain the most common volume units in chemical laboratory work, and we use these units in this book. One milliliter exactly equals one cubic centimeter; one liter exactly equals 1000 milliliters or 1000 cubic centimeters.

c. Mass and Weight The distinction between mass and weight should be clear to anyone who has seen pictures of the astronauts bounding over the surface of the moon. The gravity of the moon is smaller than that of the Earth, and so the weight of the astronauts there was less. Their bodies, however, were unchanged and had the same mass as on Earth. **Mass** is a physical property that represents the quantity of matter in a body. **Weight** is the force exerted on a body by the pull of gravity on the mass of that body.

Both the SI and metric systems rely on the gram, and the multiples and fractions of the gram, as the units for mass. The kilogram is the base unit for mass in the SI system. Strictly speaking, weight should be expressed in units of force (Section 2.8g). In practice, however, the distinction between weight and mass is often ignored.

d. Density Mass and volume are physical quantities that by themselves disclose nothing about the identity of the substance measured (both depend upon the amount of material). However, when mass and volume are combined in a ratio, they yield one of the distinctive properties of different substances (Table 2.7). **Density** is the mass per unit volume of a substance. The SI unit for density is derived from the base units of kilograms and meters, and is kilograms per cubic meter (kg/m^3). The most common unit for density is grams per cubic centimeter (g/cm^3), which is equivalent to grams per milliliter (g/mL). For example, the density of aluminum metal might be given as 2.7×10^3 kg/m^3 or 2.7 g/cm^3, the density of water as about 1 g/mL, and the density of oxygen gas (at room temperature and pressure) as 1.3 g/L. Note that the volume of a substance (especially a gas) varies with temperature and pressure. In careful work, therefore, the temperature and pressure at which a density was measured must be stated.

Table 2.6
Equivalence between Units
The equivalences marked by * are exact (see Section 2.1). Appendix II gives additional conversion factors and larger numbers of significant digits for certain ones.[a]

Length	
	1 km = 0.621 mile
	1 m = 3.281 ft
	1 cm = 0.3937 inch
	1 nm = 10 Å* = 1 mμ*
Volume	
	1 L = 1 dm^3* = 10^{-3} m^3*
	1 cm^3 = 1 mL*
	1 L = 1.0567 qt
Mass	
	1 kg = 2.205 lb
	1 g = 0.0353 oz
	1 metric ton = 10^3 kg
Energy	
	1 J = 1 kg m^2/s^2*
	1 J = 0.239 cal
	1 erg = 10^{-7} J*
	1 L atm = 101.325 J*
	1 cal = 4.184 J*
	1 eV = 1.6022×10^{-19} J
Force	
	1 dyne = 1 g cm/s^2*
	1 N = 1 kg m/s^2*
	1 N = 10^5 dyne
	1 N = 0.225 pound (force)
Pressure	
	1 Pa = 1 N/m^2* = 1 kg/m s^2*
	1 atm = 101,325 Pa*
	1 atm = 760 Torr* = 760 mmHg
	1 bar = 1 × 10^5 Pa*

[a] Å, angstrom; L, liter; eV, electron volt; atm, atmosphere; mmHg, millimeters of mercury.